

42. (NEW) The protein of Claim 41, wherein the mutation at Phe309 is a substitution.

43. (NEW) The protein of Claim 41 wherein the mutation at Phe309 is a deletion.

44. (NEW) The protein of Claim 42, wherein the mutation comprises substitution of Phe309 with Ser.

45. (NEW) A nucleic acid molecule comprising a nucleotide sequence that encodes the protein of Claim 41.

46. (NEW) An expression vector comprising the nucleic acid molecule of Claim 45.

47. (NEW) A host cell transformed or transfected with the nucleic acid molecule of Claim 45.

48. (NEW) A pharmaceutical composition comprising an effective amount of the protein of Claim 41 in admixture with a parenterally acceptable vehicle or excipient.

49. (NEW) A method for the production of a procoagulant-active protein comprising the steps of:

a) growing, in culture, a host cell transformed or transfected with the nucleic acid molecule of Claim 45; and

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b) isolating from said host cell and culture, the polypeptide product of the expression of the nucleic acid molecule.

50. (NEW) A procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification comprises a deletion of the B domain, a deletion of the von Willebrand factor binding site, a mutation at Arg740, a substitution of the Arg residue at position 336 with Ile, a substitution of the Arg residue at position 562 with Lys and an addition of an amino acid sequence spacer between the A2- and A3- domains.

51. (NEW) The protein of Claim 50, wherein the mutation comprises a substitution of Arg at position 740 with Ala.

52. (NEW) The protein of Claim 50, wherein the amino acid sequence spacer is 54 residues in length.

53. (NEW) The protein of Claim 52, wherein the amino acid sequence spacer comprises residues 741 to 794 of wild-type FVIII, wherein the residue at position 794 is selected from the group consisting of threonine and leucine.

54. (NEW) The protein of Claim 53, wherein the residue at position 794 is threonine.

55. (NEW) A nucleic acid molecule comprising a nucleotide sequence that encodes the protein of Claim 50.

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56. (NEW) An expression vector comprising the nucleic acid molecule of Claim 55.

57. (NEW) A host cell transformed or transfected with the nucleic acid molecule of Claim 55.

58. (NEW) A pharmaceutical composition comprising an effective amount of the protein of Claim 50 in admixture with a parenterally acceptable vehicle or excipient.

59. (NEW) A method for the production of a procoagulant-active protein comprising the steps of:

- a) growing, in culture, a host cell transformed or transfected with the nucleic acid molecule of Claim 55; and
- b) isolating from the host cell and culture, the polypeptide product of the expression of the nucleic acid molecule.

60. (NEW) A method of increasing binding of the protein of Claim 50 to von Willebrand factor in plasma comprising the step of introducing in plasma containing the protein and von Willebrand factor, an antibody or cross-linking agent which increases the protein's binding affinity to von Willebrand factor.

61. (NEW) The method of Claim 60, wherein the antibody recognizes an epitope at amino acids 2248 to 2285 of the protein.

62. (NEW) The method of Claim 61, wherein the antibody is ESH8.

63. (NEW) A procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification comprises a deletion of the B domain, a deletion of the von Willebrand factor binding site, a mutation at Arg740, a mutation at Phe309 and an addition of an amino acid sequence spacer between the A2- and A3-domains.

64. (NEW) The protein of Claim 63, wherein the mutation comprises a substitution of Arg at position 740 with Ala.

65. (NEW) The protein of Claim 63, wherein the amino acid sequence spacer is 54 residues in length.

66. (NEW) The protein of Claim 65, wherein the amino acid sequence spacer comprises residues 741 to 794 of wild-type FVIII, wherein the residue at position 794 is selected from the group consisting of threonine and leucine.

67. (NEW) The protein of Claim 66, wherein the residue at position 794 is threonine.

68. (NEW) A nucleic acid molecule comprising a nucleotide sequence that encodes the protein of Claim 63.

69. (NEW) An expression vector comprising the nucleic acid molecule of Claim 68.

70. (NEW) A host cell transformed or transfected with the nucleic acid molecule of Claim 68.

71. (NEW) A pharmaceutical composition comprising an effective amount of the protein of Claim 63 in admixture with a parenterally acceptable vehicle or excipient.

72. (NEW) A method for the production of a procoagulant-active protein comprising the steps of:

a) growing, in culture, a host cell transformed or transfected with the nucleic acid molecule of Claim 68; and

b) isolating from the host cell and culture, the polypeptide product of the expression of the nucleic acid molecule.

73. (NEW) A method of increasing binding of the protein of Claim 63 to von Willebrand factor in plasma comprising the step of introducing in plasma containing the protein and von Willebrand factor, an antibody or cross-linking agent which increases the protein's binding affinity to von Willebrand factor.

74. (NEW) The method of Claim 73, wherein the antibody recognizes an epitope at amino acids 2248 to 2285 of the protein.

75. (NEW) The method of Claim 74, wherein the antibody is ESH8.

76. (NEW) A procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification comprises a deletion of the B domain, a deletion of the von Willebrand factor binding site, a mutation at Arg740, a substitution of the Arg residue at position 336 with Ile, a substitution of the Arg residue at position 562 with Lys, a mutation at Phe309 and an addition of an amino acid sequence spacer between the A2- and A3- domains.

77. (NEW) The protein of Claim 76, wherein the mutation comprises a substitution of Arg at position 740 with Ala.

78. (NEW) The protein of Claim 76, wherein the amino acid sequence spacer is 54 residues in length.

79. (NEW) The protein of Claim 78, wherein the amino acid sequence spacer comprises residues 741 to 794 of wild-type FVIII, wherein the residue at position 794 is selected from the group consisting of threonine and leucine.

80. (NEW) The protein of Claim 79, wherein the residue at position 794 is threonine.

81. (NEW) A nucleic acid molecule comprising a nucleotide sequence that encodes the protein of Claim 76.

82. (NEW) An expression vector comprising the nucleic acid molecule of Claim 81.

83. (NEW) A host cell transformed or transfected with the nucleic acid molecule of Claim 81.

84. (NEW) A pharmaceutical composition comprising an effective amount of the protein of Claim 76 in admixture with a parenterally acceptable vehicle or excipient.

85. (NEW) A method for the production of a procoagulant-active protein comprising the steps of:

- a) growing, in culture, a host cell transformed or transfected with the nucleic acid molecule of Claim 81; and
- b) isolating from the host cell and culture, the polypeptide product of the expression of the nucleic acid molecule.

86. (NEW) A method of increasing binding of the protein of Claim 76 to von Willebrand factor in plasma comprising the step of introducing in plasma containing the protein and von Willebrand factor, an antibody or cross-linking agent which increases the protein's binding affinity to von Willebrand factor.

87. (NEW) The method of Claim 86, wherein the antibody recognizes an epitope at amino acids 2248 to 2285 of the protein.

88. (NEW) The method of Claim 87, wherein the antibody is ESH8.

89. (NEW) A procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification comprises a deletion of the B domain, a deletion of the von Willebrand factor binding site, a mutation at Arg740, a substitution of the Arg residue at position 336 with Ile, a substitution of the Arg residue at position 562 with Lys, an addition of an amino acid sequence spacer between the A2- and A3- domains and an antibody bound to at least a portion of the C2 domain.

90. (NEW) The protein of Claim 89, wherein the modification further comprises a mutation at Phe309.

91. (NEW) The protein of Claim 89, wherein the mutation comprises a substitution of Arg at position 740 with Ala.

92. (NEW) The protein of Claim 89, wherein the amino acid sequence spacer is 54 residues in length.

93. (NEW) The protein of Claim 92, wherein the amino acid sequence spacer comprises residues 741 to 794 of wild-type FVIII, wherein the residue at position 794 is selected from the group consisting of threonine and leucine.

94. (NEW) The protein of Claim 93, wherein the residue at position 794 is threonine.

95. (NEW) A nucleic acid molecule comprising a nucleotide sequence that encodes the protein of Claim 89.

96. (NEW) An expression vector comprising the nucleic acid molecule of Claim 95.

97. (NEW) A host cell transformed or transfected with the nucleic acid molecule of Claim 95.

98. (NEW) A pharmaceutical composition comprising an effective amount of the protein of Claim 89 in admixture with a parenterally acceptable vehicle or excipient.

99. (NEW) A method for the production of a procoagulant-active protein comprising the steps of:

- a) growing, in culture, a host cell transformed or transfected with the nucleic acid molecule of Claim 95; and
- b) isolating from the host cell and culture, the polypeptide product of the expression of the nucleic acid molecule.

100. (NEW) The protein of Claim 89, wherein the antibody binds to amino acids 2248 to 2285 of the C domain.

101. (NEW) The protein of Claim 100, wherein the antibody is ESH8.

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